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Review article

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Regulation of Bone Metabolism

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Abstract

Bone is formed through the processes of endochondral and intramembranous ossification. In endochondral ossification primary mesenchymal cells differentiate to chondrocytes and then are progressively substituted by bone, while in intramembranous ossification mesenchymal stem cells (MSCs) differentiate directly into osteoblasts to form bone. The steps of osteogenic proliferation, differentiation, and bone homeostasis are controlled by various markers and signaling pathways. Bone needs to be remodeled to maintain integrity with osteoblasts, which are bone-forming cells, and osteoclasts, which are bone-degrading cells.
In this review we considered the major factors and signaling pathways in bone formation; these include fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), wingless-type (Wnt) genes, runt-related transcription factor 2 (RUNX2) and osteoblast-specific transcription factor (osterix or OSX).

Keywords: BMP, FGF, Osteogenesis, OSX, RUNS2, Wnt

Introduction

Bone is formed through the processes of endochondral and intramembranous ossification (1). In each process mesenchymal progenitors condense and initiate developmental programs that include chondrogenesis and osteoblastogenesis (2).

During endochondral ossification, mesenchymal cells differentiate into chondrocytes, which form the cartilage growth plate. The cartilage growth plate is then gradually replaced by bone (3). Most bones in the human skeleton are made through endochondral ossification (4). These include the long, short, and irregular bones (5). Flat bones, including those of the skull, facial bones, and pelvis are made by intramembranous ossification (4-6). In this process mesenchymal stem cells (MSCs) differentiate directly into osteoblasts to organized bone (4).

In both processes, osteoblastic bone formation is identical. The synthesis of bone matrix initiates with the construction of type 1 collagen via osteoblasts. Most extracellular matrix protein of bone is type 1 collagen, which supplies strength and elasticity of bone, and scaffolding for the deposition of other matrix components such as hydroxyapatite (7).

Bone homeostasis is controlled by various signaling pathways (8). The main pathways that participate in osteoblast differentiation include members of the fibroblast growth factor (FGF) and bone morphogenic protein (BMP) families and the Wnt signaling pathway (8, 9). Correspondingly, two important transcription factors, runt-related transcription factor 2 (RUNX2) and osteoblast-specific transcription factor (osterix or OSX), are expressed in osteoblasts, both of which are essential and sufficient for osteoblast differentiation (9, 10). Some studies reported that RUNX2 and OSX are not sufficient for osteoblast maturation (11); however, it is clear that RUNX2 regulate osteogenesis (12).

Bone must be constantly replaced to preserve its strength and integrity. Bone remodeling is organized by two conflicting activities; these are bone formation by osteoblasts, which produce the organic bone matrix, and bone resorption by osteoclasts, which dissolve bone mineral and extracellular matrix (7, 13). Osteogenesis and angiogenesis are two closely-associated processes involved in bone growth, remodeling, and repair (6). Osteoclasts activate angiogenesis in vitro via expression of proangiogenic

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